DSM Anti-Infectives DSM

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852
USA

Your reference	Our reference	Direct line	Delft
	CO/SA/107	+31 15 279 2361	1999, 14 October

Docket No. 99N-1415

Dear Sirs,

Please find hereunder the comments from:

DSM Anti-Infectives (formerly Gist-Brocades B.V.)
P.O. Box 1
2600 MA Delft
The Netherlands
Contact person: Chris Oldenhof, Ph.D.
Manager International Regulatory Affairs
Tel: +31 15 2792361
Fax: +31 15 2793632

on FDA's Proposed Rule on "Supplements and Other Changes to Approved New Animal Drug Applications" (dated 23 June 1999 and issued for comments on 1 October 1999).

DSM Anti-Infectives, a Business Group of the Dutch company DSM, is one of the world's leading manufacturers of antibiotic APIs and –intermediates. Our Business Group has sixteen wholly- and partly owned manufacturing sites worldwide, and is the holder of more than twenty five DMFs (many of which were formerly approved AADAs for bulk) submitted to and in majority previously reviewed and found acceptable by the FDA.

COMMENTS:

DSM Anti-Infectives recognizes that both the existing and the proposed CFR 514.8 (b) provide for the possibility of defining less burdensome notification procedures for changes within accompanying Guidance documents.

99N-1415 C1

Gist-Brocades B.V. established at Delft, Trade Register Haaglanden No. 27227704

Because the proposed CFR 514.8 has been written in such a way that especially the recommendations on the filing mechanisms for changes to bulk pharmaceutical manufacture - which is the area our company is active in – will be covered by accompanying Guidance documents, we would like to refer to our comments previously submitted on the following Draft guidance documents:

- Draft BACPAC I Guidance
- Draft Guidance on Changes to an Approved NDA or ANDA
- Draft Guidance on Chemistry, Manufacturing and Controls Changes to an Approved NADA or ANADA

Copies of our comments on those draft documents are enclosed for your reference.
We trust that FDA will take these comments seriously into account, not only in the finalization of these Draft Guidance documents, but also, where relevant, in the finalization of the Proposed Rules.

Sincerely yours,

Chris Oldenhof, Ph.D.
Manager International Regulatory Affairs
DSM Anti-Infectives
Delft
The Netherlands

- Enclosures

DSM Anti-Infectives

DSM

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Your reference	Our reference	Direct line	Delft
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Docket No. 99D-1651

Dear Sirs,

Please find hereunder the comments from:

DSM Anti-Infectives (formerly Gist-Brocades B.V.)
P.O. Box 1
2600 MA Delft
The Netherlands
Contact person: Chris Oldenhof, Ph.D.
Manager International Regulatory Affairs
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on FDA's Draft Guidance "Guidance for Industry: Chemistry, Manufacturing and Controls Changes to an Approved NADA or ANADA" (June 1999), issued for comments early October 1999.

DSM Anti-Infectives, a Business Group of the Dutch company DSM, is one of the world's leading manufacturers of antibiotic APIs and –intermediates. Our Business Group has sixteen wholly- and partly owned manufacturing sites worldwide, and is the holder of more than twenty five DMFs (many of which were formerly approved AADAs for bulk) submitted to and in majority previously reviewed and found acceptable by the FDA.

COMMENTS:

Except for the deletion of the section on "Labeling" and for some minor differences in certain details in the text, this new Draft Guidance is very similar and largely even identical to the previously issued Draft Guidance "Changes to an Approved NDA or ANDA" (CDER, June 1999).

For this reason, our comments are exactly identical to the ones submitted on above mentioned CDER Draft Guidance. We therefore enclose a copy of these previous comments and request that these will be seriously taken into account in the further finalization of this CVM Draft Guidance.

As already stated in the enclosures, we would like to re-emphasize our serious concern that the overall approach used for all FDA's current Draft Proposed Rules and Guidances on post-approval change authorization requirements and procedures, does not take into account that it should also be possible for DMF holders to implement post-approval changes. We trust that the FDA will adhere to one of the key principles of the FDA Modernization Act: "To reduce the number of post market manufacturing changes requiring FDA approval and otherwise to make it easier to implement manufacturing changes for approved drugs". In this respect, we would also like to refer to our comments/suggestions submitted to FDAMA Docket 99N-0386 on July 26, 1999.

Sincerely yours,

Chris Oldenhof, Ph.D.
Manager International Regulatory Affairs
DSM Anti-Infectives
Delft
The Netherlands

- Enclosure

DSM Anti-Infectives DSM

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Food and Drug Administration
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Your reference	Our reference	Direct line	Delft
	CO/SA/78	+31 15 279 2361	1999, 5 July

Docket No. 99D-0529

Dear Sirs,

Please find hereunder the comments from:

DSM Anti-Infectives (formerly Gist-Brocades B.V.)
P.O. Box 1
2600 MA Delft
The Netherlands
Contact person: Chris Oldenhof, Ph.D.
Manager International Regulatory Affairs
Tel: +31 15 2792361
Fax: +31 15 2793632

on FDA's Draft Guidance "Guidance for Industry: Changes to an Approved NDA or ANDA" (June 1999).

DSM Anti-Infectives, a Business Group of the Dutch company DSM, is one of the world's leading manufacturers of antibiotic APIs and –intermediates. Our Business Group has sixteen wholly- and partly owned manufacturing sites worldwide, and is the holder of more than twenty five DMFs (many of which were formerly approved AADAs for bulk) submitted to and in majority previously reviewed and found acceptable by the FDA.

COMMENTS:

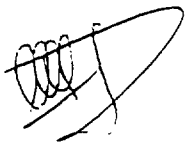
The content of this new FDA Draft Guidance has caused great disappointment and even astonishment within our company. However, we believe this may have been caused by the fact that this new Guidance has probably been drafted before the FDA had the opportunity to evaluate the comments which have been previously submitted by industry - including our company - on the Draft BACPAC I Guidance, that was issued in November 1998.
For your reference, we enclose a copy of our comments on the BACPAC I Draft Guidance, which were submitted in January 1999.

We trust that the FDA will endorse our view that Regulations and/or Guidance that do not offer industry the possibility to maintain its regulatory compliance, should not come into existence. However, as was clarified in our enclosed comments, the BACPAC I Draft unfortunately is a clear example of such a, to be omitted, Guidance.
The now issued Draft Guidance on "Changes to an Approved NDA or ANDA" contains exactly the same elements, relating to the authorization of changes in bulk pharmaceutical manufacture, as the BACPAC I Draft did. It, therefore, unfortunately falls within the same, to be avoided, category.

We kindly request the FDA to once more seriously consider the points made and the suggestions given under point 2. ("Major specific comment") in our enclosed letter of last January. With these comments we intended to cover not only BACPAC I, but indeed the entire scope of BACPAC.

We hope and trust that both this new Guidance and its companion BACPAC Guidance will, in their final form, provide for procedures and requirements that will enable industry to implement necessary, beneficial and often unavoidable changes in bulk pharmaceutical manufacture. However, in order to avoid that many API manufacturing processes will be completely and perpetually "frozen", both Draft Guidances will require further revision along the lines suggested in the enclosure.

Sincerely yours,



Chris Oldenhof, Ph.D.
Manager International Regulatory Affairs
DSM Anti-Infectives
Delft
The Netherlands

- Enclosure

Courtesy copy:
Dr. Roger Williams (HFD-003)
Deputy Center Director for Pharmaceutical Science
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Gist-brocades
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OUR REF CO/SA/256

YOUR REF

DATE January 6, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852
USA

Docket No. 98D-0994

Dear Sirs,

We herewith would like to submit the comments of:

Gist-Brocades B.V
P.O. Box 1
2600 MA Delft
The Netherlands
(contact person: Dr. Chris Oldenhof)

on the Draft Guidance for Industry "BACPAC I", issued by the FDA in November 1998.

Gist-Brocades B.V. is one of the world's leading manufacturers of antibiotic APIs and -intermediates. Our company has twelve wholly- and partly owned manufacturing sites world wide, and is the holder of more than twenty DMFs (many of which were formerly approved AADAs for bulk) submitted to and in majority previously reviewed and found acceptable by the FDA.

1. General statement:
(Relating to the entire Draft Guidance)

The current FDA thinking reflected in the BACPAC I Draft Guideline is one very positive an important step towards improving post approval change requirements, procedures, and filing mechanisms for APIs and their intermediates in such a way that they will accommodate change, progress and improvements instead of making any change practically impossible, as has largely been the case for dedicated bulk manufacture until now. The adherence to scientific principles - such as substance "equivalence" as key criterion - is strongly supported by Gist-brocades.

The most critical issue which is, however, left unaddressed by the Draft Guidance relates to the procedural problems which exist for implementing - especially process - changes in Multi-Customer and/or Long-Chain Supply Systems (MCLCSS). The paragraphs in the Draft Guidance relating to changes in site, scale and equipment, however, have largely been received by us as being realistic, reasonable and workable.
Our specific comments follow hereunder.

2. **Major specific comment:**
(Relating to page 14, line 99 to page 18, line 38 of the Draft Guidance)

Because an important part of the API- and intermediates manufacturing industry is involved in the supply within MCLCSSs, we strongly feel that the key issue still to be solved through BACPAC lies in preventing that manufacturing changes will be unnecessarily and fully blocked for reasons of a too high regulatory burden - in terms of efforts, costs - on purchasing companies downstream.("The Customers, The Customers' Customers and even The Customers' Customers' Customers" may be involved in efforts related to submissions of (A)NDA Supplements!).
Therefore, our by far most important comment is the following:

* If, within the scope of BACPAC I, equivalence has been proven for any intermediate (up to and including the final intermediate), the submission of a supplement by the holder(s) of related (A)NDAs will not be required.
  Reference to the changes relating to the manufacture of the intermediate should be provided within the (A)NDAs' Annual Reports.

In brief, our comment comes down to downgrading all process changes with proven "intermediate equivalence" to the Annual Reporting category (CFR 314.70.d.)
Note: The section of the Guidance describing these specific requirements should strongly emphasize that equivalence determinations which appear to be inadequate may lead to severe sanctions up to product recalls. It should also stress that the scrutiny of all data relating to the determination of equivalence will be a top priority within FDA's bulk inspections program.

The above filing mechanism forms the only thinkable procedure for making process improvements possible within MCLCSSs, as long as the approval of DMFs is not yet an option for the FDA and as long as assessment of any information included in DMFs and in their Amendments can only be triggered through each and every related (A)NDA separately.

However, approval of DMFs is still an extremely suitable option to solve the MCLCSSs issue. Such a system, which then should include approval of submissions on changes to the DMFs, would result in a workable situation for both the FDA and for industry. To ensure both workability and the safety of drug products, the system should have the following features:
- Only DMFs referenced by (A)NDAs will be assessed and approved
- Approval may be limited to one or more SUPAC dosage form categories.

Overall, such a procedure would increase regulatory control over many process changes: review may occur before implementation instead of after implementation, as is the case with CBES changes.

We would like to suggest yet one other possible solution for the above issue, from a quite different angle of approach:
In MCLCSSs the final intermediates are normally older, well known substances, available from a substantial number of suppliers. It may therefore be concluded that such substances are falling within the criteria, as included in FDA's February 1987 Guidance, to determine what should be the "Starting Material". This because clearly more than one of the listed criteria are being met by such materials.
In addition, this would be fully in line with the current (draft 2) definition on the "API Starting Material" within ICH/Q7A.

By clarifying this matter, possibly within the BACPAC Guidance, the "Long Chain" aspect of the above described issue on filing mechanisms could also be resolved in a straightforward and elegant way.

3. Additional major comment:
(Relating to page 12, line 54 to page 14, line 98 of the Draft Guidance)

The Draft Guidance indicates that in case of relaxation or deletion of specifications other than for the final intermediate, the filing mechanism should be CBES. However, obviously such a requirement will lead to exactly the same filing problems in MCLCSSs as described above.
We therefore analogously propose to either allow for filing of such changes in Annual Reports, PROVIDED THAT EQUIVALENCE OF AN INTERMEDIATE HAS BEEN PROVEN, or alternatively, to consider adopting the suggestion on the "Starting Material" definition, as described above.

4. Minor comments:

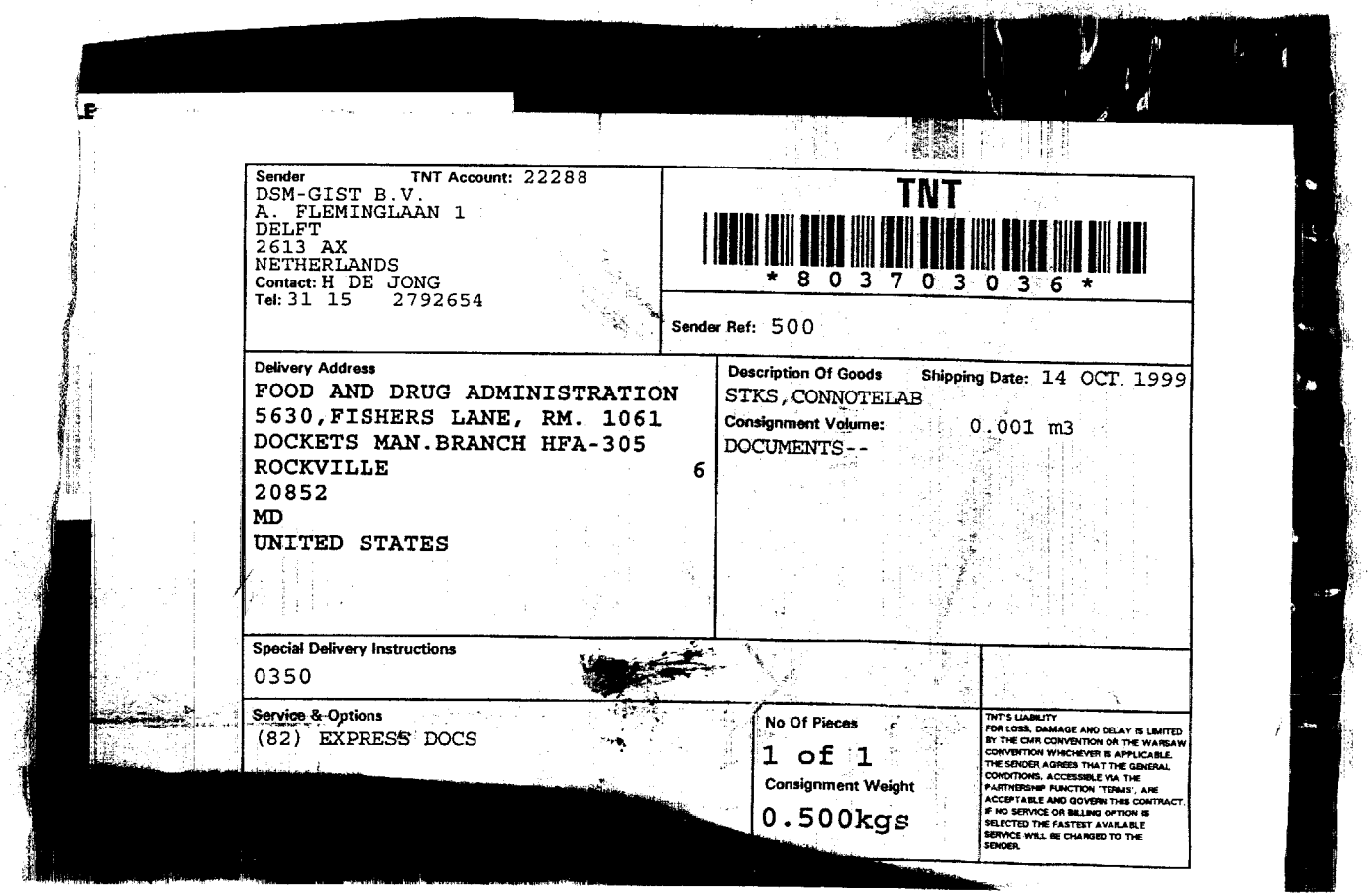
(Relating to page 3, line 76 of the Draft Guidance)
We suggest to delete "at a minimum" in order to avoid unclarity and uncertainty.

(Relating to the section starting from page 8, line 32 of the Draft Guidance)
For the sake of clarity, we would propose to insert an introductory sentence to that section as follows:
"If the site change is not within a single facility, the following applies:"

We trust that the FDA will recognize the very urgent need to resolve the final major issues within the area of regulatory filings on bulk post approval changes, as described above. The BACPAC Guidance is offering the unique opportunity for accomplishing such a historic result.
It is our strong belief that only reasonable and, especially also workable procedures and filing mechanisms will bring benefit to society as a whole and to the safety and health of the patients in particular.

Sincerely yours,

Chris Oldenhof, Ph. D.
Manager International Regulatory Affairs
Gist-Brocades B.V.
Delft
The Netherlands



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Description Of Goods Shipping Date: 14 OCT 1999
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Consignment Volume: 0.001 m3
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Special Delivery Instructions
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No Of Pieces
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